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EXCRETION OF 17-HYDROXYCORTICOSTEROIDS, CATECHOL AMINES,
AND UROPEPSIN IN THE URINE OF NORMAL PERSONS AND DEAF SUBJECTS
WITH BILATERAL VESTIBULAR DEFECTS FOLLOWING ACROBATIC FLIGHT STRESS

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SUMMARY PAGE

THE PROBLEM

One aspect underlying the release of catechols and steroids as indicators of flight stress which has not previously been investigated concerns the role of the vestibular organs in such release. The purpose of the present report is to demonstrate that these organs must be taken into account.

FINDINGS

Six men with labyrinthine defects and eleven normal subjects were exposed to flight stress in an AD5 aircraft in an effort to determine the role of the vestibular organs in the excretion of catechols and steroids. Chemical measurements revealed that a significant increase in excretion of these stress hormones occurred in response to flight stress in case of the normal but not of the L-D subjects which must have been attributable to the presence and absence, respectively, of the sensory organs of the inner ear. No significant changes in release of uropepsin were observed for either group.

It is concluded that the vestibular organs must be taken into account in evaluating the effects of actual and simulated flight stresses where the gravitational inertial force environment is a variable.

ACKNOWLEDGMENTS

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INTRODUCTION

The history of investigations on flight stress using catechols and steroids as indicators is comparatively brief but revealing (2,4;6-10; 14-16; 18-25). It has been demonstrated that epinephrine, norepinephrine, and secretions of the adrenal cortex are released as a result of the interactions between the flyer and stressful factors arising out of his task and environment. Epinephrine, especially that stored in the medulla, may be quickly released; that its release is mainly dependent on psychological factors is declared 1) by its appearance prior to flight (6), 2) by a sometime lack of proportionality to physical stress (20), and 3) by the phenomenon of habituation (7). The secretion of norepinephrine, mainly released at the sympathetic nerve endings, need not parallel that of epinephrine; it is closely related to stressful factors affecting physiological responses but not to anticipation of or anxiety during flight (6).

These findings are supported by the results of investigations utilizing a human centrifuge. It has been shown 1) that "mock acceleration" was equivalent to a high level of centripetal force for the release of epinephrine but not norepinephrine (10); 2) that the increase in norepinephrine was proportional to the level of G force while the increase in epinephrine was not (9); 3) that on repeatedly exposing subjects to moderate levels of accelerative force the release of epinephrine declined but no habituation was demonstrable in the output of norepinephrine (7); and 4) that the affect states anxiety and aggression were associated, respectively, with relatively low G tolerance-high epinephrine release and relatively high G tolerance-high norepinephrine release (3,26).

Investigators utilizing adrenal cortical hormones or their metabolites as indicators have demonstrated increased secretion in response to such factors in flight as the force environment (25), amount of danger (18), duration of exposure (25), the degree of responsibility placed on the flyer (18,19), and his "susceptibility to fatigue (25)." There is good evidence that a hierarchy exists in rank order of factors affecting these secretions (20,25). Moreover, there are hints of differential secretions of these hormones and that they need not parallel the release of epinephrine and norepinephrine (20).

One aspect underlying the release of these "stress hormones" which has not been investigated concerns the role of the vestibular organs, and it is the purpose of this report to demonstrate that they must be taken into account.

PROCEDURE

SUBJECTS

The clinical findings and results of functional tests of auricular sensory organs in the six men with labyrinthine defects, hereafter termed L-D subjects, are summarized in Table I. The normal group was comprised of eleven men on active duty in the Navy. Six of the eleven were medical students serving as "summer residents." The remaining

TABLE I

| CLINICAL FINDINGS AND RESULTS OF FUNCTIONAL TESTS OF AURICULAR ORGANS OF SIX SUBJECTS WITH LABYRINTHINE DEFECTS | | | | | | | |
|--|-----|----------|--------------|---------|-----|------------------|------------------|
| SUB. | AGE | ETIOLOGY | AGE ONSET | HEARING | | CALORIC TEST* | |
| | | | | R | L | R | L |
| ST | 20 | MEN | 12½ | 130 | 135 | ¹ NEG | ¹ NEG |
| GU | 21 | MEN | 4½ | 145 | 145 | ² NEG | ³ NEG |
| PI | 22 | MEN | 3 | NIL | NIL | NEG | NEG |
| ZA | 20 | MEN | 3½ | 135 | 130 | NEG | NEG |
| MY | 25 | MEN | 8 | NIL | NIL | NEG | NEG |
| GR | 48 | MAS | 12 | NIL | NIL | NEG | NEG |

*NO VERTIGO OR OBSERVABLE NYSTAGMUS WHEN TYMPANUM IRRIGATED WITH COLD WATER (4.5-6°C). NYSTAGMOGRAMS DURING IRRIGATION FOR THREE MINUTES: 1? VERTICAL NYSTAGMUS, 2? NYSTAGMUS, 3. MINIMAL NYSTAGMUS.

five subjects had been aviation training candidates but at the time of the experiment were awaiting release from the flight training program; they had not yet entered the flight phase, and the reasons for their release did not vitiate their use as subjects.

FLIGHT STRESS

The flight procedure (Figure 1) was carried out in an AD5 aircraft with a veteran Navy research pilot at the controls. The same sequence was followed on each flight, as follows: Take-off and climb to 12,000 feet, 360 degree turn at 60 degree bank to left and right (2.0 to 2.5 G), wingover to left and right, three aileron rolls to the left, barrel roll to left and right, three aileron rolls to the left, barrel roll to left and right, and a split S coming out at approximately 5,000 feet at 4Gs. The sequence was carried out in a continuous manner so that the aircraft was in straight and level flight for only very short periods of time. If, at the end of the first sequence, the subject was ill, the aerobatics were discontinued and the pilot returned the plane to the field. If vomiting was not imminent, the pilot climbed back to 12,000 feet and repeated the same procedure. These two sequences required approximately thirty minutes.

METHODS

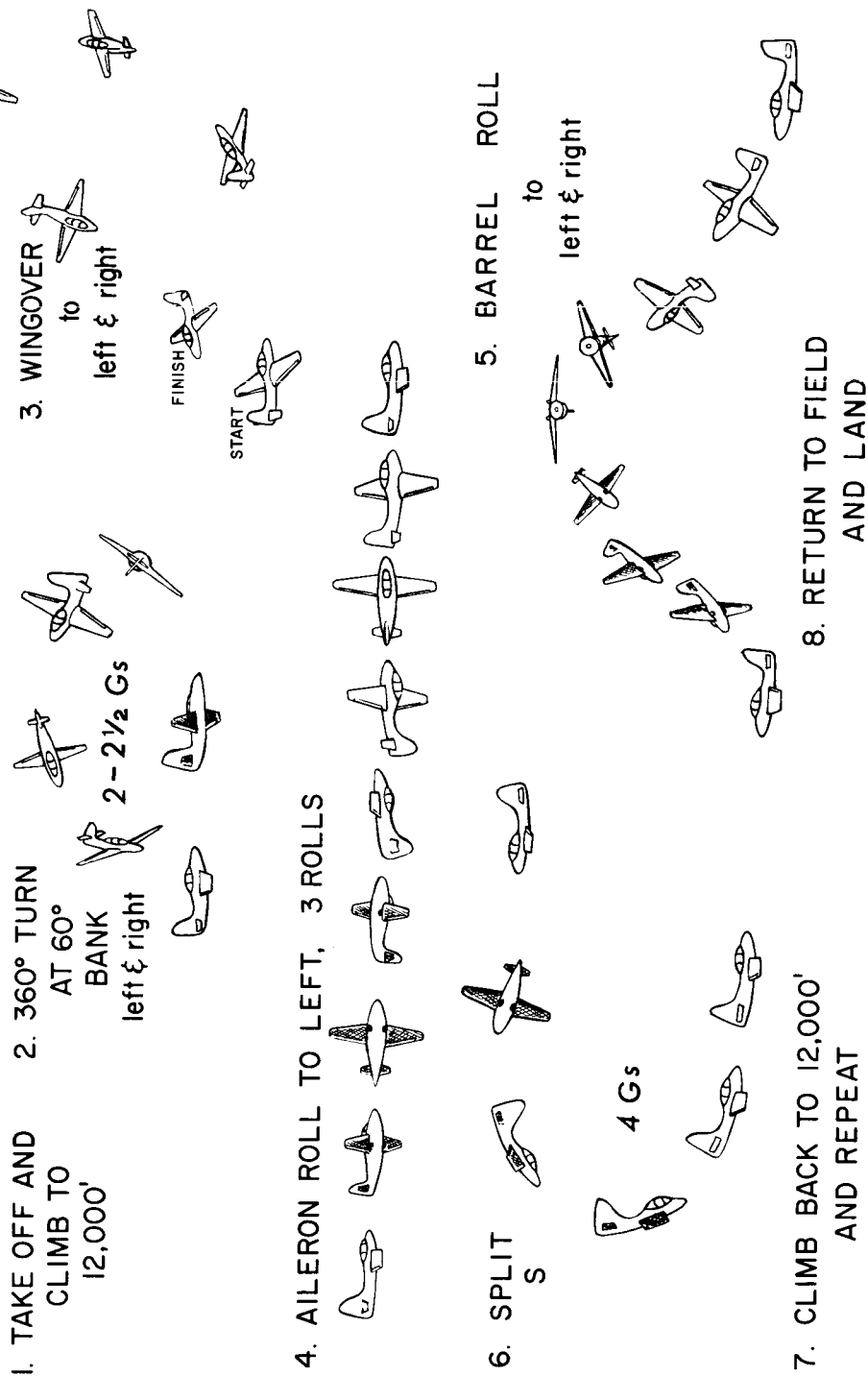
Account was taken of the fact that excretion of adrenal hormones varies widely among individuals and also has a diurnal pattern. Adrenal activity appears to be lowest during the night resting hours as measured by urinary levels. Also, from preliminary experiments similar to the one reported on here, it was observed that practically all of the increase in amines and steroids was excreted in a six-hour period following the single stressful incident. In order to take these factors into consideration, the results for the normal and vestibular defective groups are tabulated separately with each acting as its own control.

Two urine samples were collected on each of two days as follows: 1) a night "resting" sample and 2) a six-hour "afternoon" sample on the day prior to flight and again on the flight day. Diet was not regulated except that adequate fluid intake was encouraged to ensure sufficient urine volume. All subjects were instructed to get adequate rest and to avoid vigorous physical activity during the test and control days.

Each voiding of the urine was split into two approximately equal portions. One was acidified (pH 1-2) with enough 6N sulfuric acid to stabilize the catechol amines and then was quick frozen; the other portion was used for the steroid and uropepsin determinations and was frozen without stabilizers inasmuch as they are stable under these conditions.

The catechol amine determinations were carried out using the method of Crout (5), and Kornel's glucuronidase hydrolysis method (17) was used for the steroids. The excretion rates of the adrenal hormones were expressed as micrograms per hour. Anson's method (1) as modified by Gray et al. (11) was used for the uropepsin determination and these results were expressed as units per hour.

FIGURE 1



FLIGHT SEQUENCE

RESULTS

With regard to the clinical symptomatology, none of the L-D subjects expressed concern prior to flight and none manifested symptoms of motion sickness during flight. Four of the normal subjects expressed moderate concern prior to flight, and in three instances the flight was terminated because of motion sickness; symptoms in the case of the fourth subject were nil. The remaining seven subjects expressed minimal concern prior to flight; one became sick and the flight was terminated; four experienced moderate malaise, and one of these "blackened out" on two occasions; and two reported slight malaise.

The results of the chemical measurements are summarized in Table II and Figure 2. The normal subjects released a significantly larger amount of catechols and steroids on the afternoon of the flight compared with the nonflight day; there were no significant differences between the resting samples on the two days. The L-D subjects did not release a significantly larger amount of catechols and steroids on the two afternoons; they did release a larger amount of norepinephrine during the night prior to flight than on the control day. No significant differences in release of uropepsin were observed between flight and nonflight days for either group. Although Gray and colleagues (11) found that uropepsin values increased with an increase in adrenal cortical activity in chronic stress or in certain pathological conditions, there were no demonstrable changes in our experiment where the stress was limited to one brief exposure.

DISCUSSION

Insofar as the normal and L-D subjects are representatives of their groups, the striking difference in response to flight stress must be attributable to the presence and absence, respectively, of the sensory organs of the inner ear. While our experimental design could not distinguish between the relative roles of the auditory and vestibular organs, the greater importance of the latter may be accepted on a priori grounds. If this assumption is allowed, it follows that all of the flight stresses except those directly or indirectly mediated by the vestibular organs were insufficient to cause symptoms or release the stress hormones in the L-D subjects. These stresses included the effects of constraint, slight anoxia, all except the vestibular effects of the force environment, and whatever effects were generated by nonphysical factors such as danger and concern over the unknown. With regard to the force environment, there was an almost continual change in the acceleration pattern affecting the sympathetic nerves involved in circulatory adjustments, a mechanism to which von Euler and Lundberg (6) drew attention in attempting to explain the release of norepinephrine in test pilots. It would also follow that their lack of concern prior to flight and absence of anxiety during flight were indirectly related to their labyrinthine defects, possibly on the basis of insusceptibility to motion sickness (12). The fact that none blacked out is of interest in view of the possible relation between high blackout threshold and high norepinephrine level (27).

TABLE II

STATISTICAL EVALUATION OF URINARY STRESS HORMONE LEVELS IN NORMAL AND VESTIBULAR DEFECTIVE SUBJECTS AFTER ACROBATIC FLIGHT

Mann-Whitney "p" Values

| | Resting (NF) vs | | | Resting (FD) vs | | | Resting (NF) vs | | | Afternoon (NF) vs | | |
|------------|--------------------|-----|-----|--------------------|------|------|--------------------|-----|-----|----------------------|-----|-----|
| | Afternoon (NF) | | | Afternoon (FD) | | | Afternoon (FD) | | | Afternoon (FD) | | |
| | E | NE | T | E | NE | T | E | NE | T | E | NE | T |
| NORMAL | >.1 | >.1 | >.1 | .005 | .005 | .005 | >.1 | >.1 | >.1 | .05 | .05 | .05 |
| VEST. DEF. | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 |

CATECHOL AMINES

| | F | | | C | | | TC | | |
|------------|--------------|-----|-----|--------------|------|------|----------------|-----|-----|
| | RESTING (NF) | | | RESTING (FD) | | | AFTERNOON (NF) | | |
| | F | C | TC | F | C | TC | F | C | TC |
| NORMAL | >.1 | >.1 | >.1 | .01 | .005 | .005 | >.1 | >.1 | >.1 |
| VEST. DEF. | >.1 | .05 | .04 | >.1 | .005 | .005 | >.1 | >.1 | >.1 |

17-OH CORTICOSTEROIDS

| | TU | | | TU | | | TU | | |
|------------|--------------|-----|-----|--------------|-----|-----|----------------|-----|-----|
| | RESTING (NF) | | | RESTING (FD) | | | AFTERNOON (NF) | | |
| | F | C | TC | F | C | TC | F | C | TC |
| NORMAL | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 |
| VEST. DEF. | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 |

UROPEPSIN

| | TU | | | TU | | | TU | | |
|------------|--------------|-----|-----|--------------|-----|-----|----------------|-----|-----|
| | RESTING (NF) | | | RESTING (FD) | | | AFTERNOON (NF) | | |
| | F | C | TC | F | C | TC | F | C | TC |
| NORMAL | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 |
| VEST. DEF. | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 | >.1 |

E = epinephrine
NE = norepinephrine
T = total catechol amines

F = free 17-OH corticosteroids
C = conjugated 17-OH corticosteroids
TC = total 17-OH corticosteroids

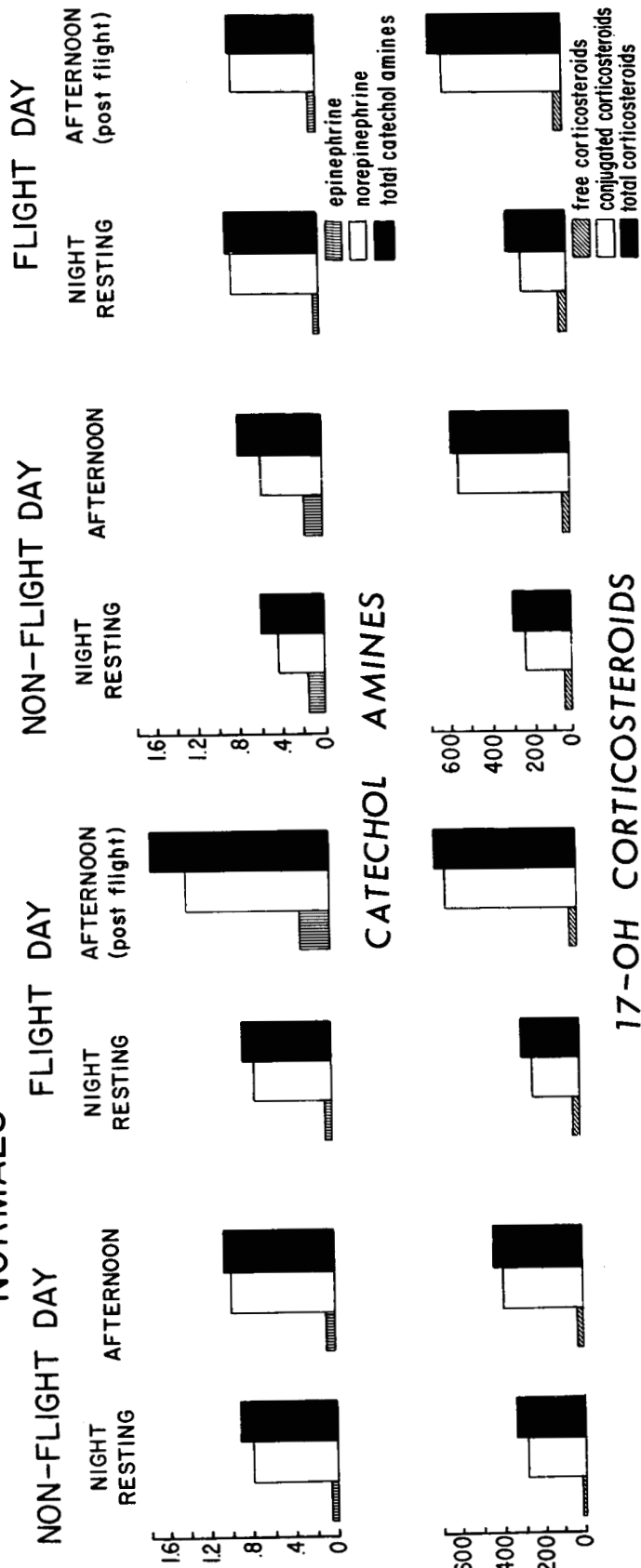
TU = total uropepsin
NF = non flight day
FD = flight day

FIGURE 2

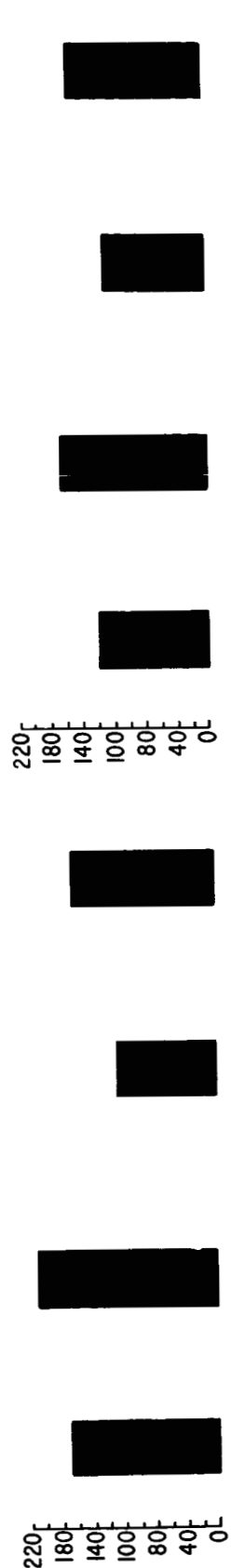
STRESS HORMONE EXCRETION AFTER ACROBATIC FLIGHT

VESTIBULAR DEFECTIVE

NORMALS



17-OH CORTICOSTEROIDS



Inasmuch as the normal subjects were exposed to the same environmental factors as the L-D subjects, their response as indicated by the increased excretion of the stress hormones during flight must have been the result of unusual vestibular stimulation acting on neurohormonal mechanisms and whatever stresses were generated as the result of past conditioning. Our experiment does not provide for the separation of these two factors, but in all likelihood both were of etiological significance; some of the normals approached the flight with moderate concern which was not properly explicable on the basis of any danger involved but was based on anticipation of an unpleasant experience. The fact, however, that this was not reflected in a measurable release of epinephrine prior to flight indicates that "anticipation" was not of great significance.

It cannot be assumed that the small number of normal and L-D subjects are fully representative of their groups. On another occasion the opportunity arose to expose an L-D subject who suffered from acrophobia to the same test flight. He was extremely anxious both before and during flight, but he did not manifest typical symptoms of motion sickness. The urine epinephrine increased 700 per cent over the control value. This indicates, if it does not prove, that the release of this catechol may be almost entirely of psychogenic origin. With regard to normal subjects the relatively small release of the stress hormones in the case of the astronauts (23, 24) indicates the importance of the human variable in its interaction with environmental stress. At the other extreme, in at least two of the normal subjects psychogenic factors were a cause of symptoms under less stressful conditions in another experiment (13).

The general conclusion from this study is that the vestibular organs must be taken into account in evaluating the effects of actual and simulated flight stresses where the gravitational inertial force environment is a variable. Their effects may be the direct result of unusual stimulation or the indirect result of past conditioning.

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